chemokine, and recovering said chemokine.

Please add new claims 14 and 15.

14. (New) A host cell transfected with a recombinant Sendai virus vector expressing a chemokine.

15. (New) A method of inhibiting HIV proliferation which comprises,

incubating the host cell of claim 14 in vitro to allow chemokine secretion; and

contacting said chemokine with cells that are infected with HIV.

Support for the Amendments

Support for claim 14 is found at the paragraph bridging pages 7 and 8 and Example 1 of the specification. Support for claim 15 is found in Example 4 at pages 11-14.

REMARKS

Responsive to the Office Action of April 14, 1999, (Paper No. 5), Applicants hereby request reexamination of the application, as amended herein, and reconsideration of the claims. Claims 1-13 were examined in the case. All claims stand rejected. The present response cancels claim 13 and adds new claims 14 and 15. Each of the objections and rejections levied in the Office action is addressed individually below.

Lack of Enablement

Claims 9 and 11-13 stand rejected for lack of enablement under U.S.C 112, first paragraph. The Examiner states that the "Applicants have provided no teachings or examples specific to in vivo gene therapy." The Applicants respectfully disagree.

As described above, claim 13, directed to a method of inhibiting HIV proliferation by infecting HIV-infected cells with a recombinant Sendai virus vector expressing a chemokine, has been canceled. Thus, the rejection of claim 13 is moot.

Claim 9 is directed to a method of treating HIV using gene therapy. Claims 11 and 12 are directed to pharmaceutical compositions comprising recombinant Sendai virus vectors expressing SDF-1α or SDF-β for use in gene therapy. Applicants would like to point out that these claims are supported by the description at page 8, line 13 to page 9 line 6 in the specification. From this description, one of ordinary skill in the art could readily practice the claimed invention

It has been established that the specification need not explicitly teach every possible embodiment of the invention. As stated in *Scripps Clinic & Research Foundation v. Genentech, Inc.*, "the purpose of [the enablement] provision is to assure that the inventor provides sufficient information about the claimed invention that a person of skill in the field of the invention can make and use it without undue experimentation, relying on the patent specification and the knowledge in the art," See, 18 USPQ2d 1896, 1006 (Fed. Cir. 1991). The teachings of the specification and the knowledge in the art at the time the invention was made provide all of the experimentation necessary for one of ordinary skill in the art to routinely determine the parameters required for successful administration of the recombinant Sendai virus or SDF-1 for

treatment of HIV infection without undue experimentation. The fact that gene therapy is an emerging technology does not mean that the particular invention claimed and described in the present case is not enabled. The Examiner has pointed to no information that would be needed to practice the claimed invention that would require undue experimentation to determine. This rejection shall be withdrawn.

Indefiniteness

Claims 4, 5 and 11-13 stand rejected under U.S.C. 112, second paragraph for indefiniteness. The Examiner questions the meaning of the "disseminative" and "not disseminative".

Claim 13 has been canceled rendering this rejection moot.

Applicants would like to clarify the meaning of these terms by directing the Examiner's attention to page 4, lines 9-13 of the specification where the term "disseminative capability" is defined as "the capability to form infectious particles or their equivalent complexes and disseminate them to other cells following the transfer of nucleic acid into host cells by infection or artificial techniques and the intracellular replication of said nucleic acid." In contrast, "not disseminative" is meant to refer to a virus that is incapable of forming infectious particles or their equivalent complexes and disseminate them to other cells. Therefore, the meaning of these terms is clear in light of the definition provided in the specification.

Obviousness

Claims 1-8 and 11-13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over either of Hasan et al. (1997) or Yu et al. (1997), in view of both of Bleul et al., (1996) and Calain et al., (1993).

Hasan et al. and Yu et al. teach the use of recombinant Sendai virus for expressing firefly luciferase and gp 120, respectively. Hasan et al. discloses that the luciferase gene products were inactivated, probably due to extensive aggregation in cells, and that an increase in genome length retarded virus replication and resulted in a several fold decrease in virus yield. Hasan et al. refers to the Yu et al. reference and discloses that the SeV recombinant having the gp 120 gene, which is only slightly shorter than the luciferase gene, displayed a very similar attenuated phenotype to that of Sev/luc (page 2819, line 8-31). These references combined do not suggest the claimed invention.

The present specification discloses that 1) recombinant highly basic polypeptides or peptides such as chemokines are produced in *E. coli* with low productivity; 2) *E. coli*-based production generally requires extensive, multi-step purification of the product before use; 3) extensive aggregation is often inevitable, particularly for such basic polypeptides as chemokines; and 4) the substitute process for recombinant production, chemical synthesis, is not only laborious, requiring careful refolding, but is also expensive (page 2, lines 19-30). Moreover, no report of the purification of recombinant chemokines produced in mammalian and other higher vertebrate cells by recombinant viruses was available at the time the claimed invention was made.

Under these circumstances, it would not have been obvious to one of ordinary skill in the art that chemokines could be efficiently produced using a Sendai virus vector even if firefly luciferase and gp 120 were produced using the same vector. The Applicants are the first to succeed in producing recombinant chemokines with inhibitory activity of HIV replication in substantial amounts (10 μg/ml or more for the SDF-1α, see page 11, lines 8-11 of the specification), which can be simply and economically be purified by heparin column chromatography (Example 3 at page 11).

Bleul et al. teaches anti-HIV activity of SDF-1, which Applicants acknowledge was in the art; this is not central to the inventive contribution, as described above. Calain et al. teaches the use of centrifugation to recover the Sendai virus nucleocapsids, also not relevant to the inventive contribution. The claimed invention would not have been obvious over the primary references even if they were combined with the teachings of Bleul et al. and Calain et al.

Claim 10 stands rejected under U.S.C. 103(a) as being unpatentable over Bluel et al., Hasan et al. And Hasegawa et al.

As discussed above, one skilled in the art could not have readily expected the efficient production of recombinant chemokines with a Sendai virus vector. Therefore, it would not have been expected that the recombinant chemokines produced by the method of the present invention could be functionally authentic and could inhibit HIV replication. Hasegawa et al. teaches the use of a recombinant Sendai virus in gene therapy, but does not overcome the deficiencies of the primary reference. Even in view of the teaching of Hasegawa et al., the claimed method would not have been obvious to one skilled in the art.

CONCLUSION

Applicants would like to thank the Examiner for thoughtful analysis of this case. Applicants respectfully request reconsideration of the pending claims as amended. Based on the arguments presented above, it is submitted that the claims, as amended herein, are allowable over the prior art of record and in condition for allowance.

Please charge any fees that may be required to our Deposit Account No.03-2095.

Respectfully submitted,

Date: August 13, 1999

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